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The outcome of COVID-19 in patients with hematological malignancy

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Summary

Objective The aim of this study was to examine the effect of coronavirus disease 2019 (COVID-19) on the malignancy-related clinical course and overall survival, and to determine the factors affecting mortality. **Methods** This retrospective study included 77 patients with hematological cancer and COVID-19. Patients were sub-grouped for analysis as survivors and non-survivors.

Results COVID-19 was seen more frequently in myeloproliferative neoplasms (MPN), non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) patients. Mortality rate due to COVID-19 was 20.8%. No statistically significant difference was determined between the survivor and non-survivor groups with respect to age and gender, presence of any comorbidity, leukocyte, neutrophil, lymphocyte, and monocyte values. Platelet count and hemoglobin count were signifi-

cantly lower in the group with mortality than in the group with recovery.

Conclusion It should be kept in mind that low hemoglobin and platelet levels contribute to mortality. In addition, it is important to protect patients with hematological cancer from COVID-19 and undertake effective vaccination due to its mortal course.

Keywords Cancer · Coronavirus disease 2019 · Hematological malignancies · Platelet count · Hemoglobin

Introduction

Coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization (WHO) on 11 March 2020 [1]. Patients with comorbidities such as hypertension (HT), cardiovascular disease, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and cancer are at greater risk of COVID-19 infection and have worse clinical outcomes [2, 3]. Immunosuppression is an important risk factor for COVID-19 disease. Previous studies have shown the prevalence of cancer in COVID-19 patients to be 2% [4], 3.7% of patients with COVID-19 are immunodeficient [5, 6].

The survival of patients with hematological malignancies has increased due to improved treatment options and better medical care. However, immunosuppression in these patients resulting from both the biology of the disease and the treatments may have an adverse effect on the course of COVID-19. In this context, infections impair the quality of life of patients and even increase mortality [7].

The aim of this study was to evaluate patients who were being followed up for malignant hematological diseases and developed COVID-19, to examine the effect of the COVID-19 infection on the malignancy-re-

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lated clinical course and overall survival and to determine the factors affecting mortality.

Patients and methods

This retrospective study included patients with a history of malignant hematological disease and COVID-19 who were followed up in the Hematology Department of Diskapi Yildirim Beyazit Training and Research Hospital. Nine specific types of hematological malignancies were examined: acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphoid leukemia (CLL), myelodysplastic syndrome (MDS), hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), multiple myeloma and Philadelphia chromosome (Ph) negative myeloproliferative neoplasms (MPN).

Patients who presented at the hematology clinic between 01 April 2020 and 31 December 2020 and had a history of COVID-19 infection participated in the study. A confirmed COVID-19 diagnosis was accepted as positivity in the polymerase chain reaction (PCR)-based test of a specimen on a nasopharyngeal swab or typical findings on thorax computed tomography (CT). Data for analysis in the study were retrieved from hospital records, Public Health Management System (HSYS) patient files and the MERNIS death notification system.

Demographic and clinical information about both hematological disease and COVID-19 were recorded. Diagnosis, disease status which was classified in 4 groups as initial diagnosis, remission, stable, or relapsed/refractory disease and treatment protocols were recorded for the hematological disease. For COVID-19, symptoms, severity of infection, hospitalization, need for mechanical ventilation or intensive care, COVID-related treatments and mortality were recorded. COVID-19 severity was defined as mild (outpatient), moderate (hospitalization) or severe (ICU).

Patients were sub-grouped for analysis as hospitalized and non-hospitalized and survivors and non-survivors. These groups were compared with each other, in respect of the characteristics related to the clinical course of COVID-19 and the data related to the hematological disease.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS Statistics 27.0 software (IBM, Armonk, NY, USA). Descriptive data were stated as median and range, mean \pm standard deviation (SD) values, or number (*n*) and percentage (%). Conformity of the data to normal distribution was assessed with the Kolmogorov–Smirnov test. The independent samples *t*-test and the Mann–Whitney *U*-test were used in the analysis of quantitative independent data. The χ^2 test

was applied in the analysis of qualitative independent data, and the Fisher test when χ^2 test conditions were not met. A value of $p < 0.05$ was accepted as statistically significant.

Results

Evaluation was made of 77 patients with COVID-19 infection, who were being followed up in our clinic for a diagnosis of hematological malignancy. The patients comprised 40 (51.9%) males and 37 (48.1%) females with a median age of 60 years (range 27–93 years). At least one comorbidity was determined in 46 (59.7%) patients, primarily HT (*n*:28), DM (*n*:22) and COPD (*n*:14). The demographic and clinical characteristics of the patients are given in Table 1.

The COVID-19 diagnosis was based on PCR test positivity in 67 (87.0%) patients; in 10 (13.0%) patients, the PCR test was negative and the diagnosis was confirmed from CT scan findings.

COVID-19 was seen more frequently in patients with MPN (22.1%), NHL (19.5%) and MM (15.6%). Active treatment of chemotherapy, immunotherapy or immunosuppressive therapy were being received by 43 (55.8%) patients. The most common treatments were hydroxyurea (HU), R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine, prednisone) chemotherapy regimen and lenalidomide and dexamethasone with one of the proteasome inhibitors. The data of the hematological diagnoses of the patients are shown in Table 2.

When the clinical course of COVID-19 was examined; 56 (72.7%) patients were symptomatic and the most common symptoms were fever (81%), cough (74%) and weakness (69%). Hospitalization was required by 39 (50.6%) patients and median duration length of stay in hospital was 8 days (range 2–30 days). Intensive care was required by 16 patients, all of whom were intubated. The most used agents in the treatment of COVID-19 infection were favipiravir and hydroxychloroquine. Details of the clinical course of COVID-19 and the treatments applied are given in Table 1.

Mortality due to COVID-19 infection developed in 16 patients, giving a mortality rate of 20.8%. The median time from COVID diagnosis to death was 8 days (range 3–53 days). The hematological diagnoses of the exitus patients were 2 AML, 3 MPN, 2 MM, 4 CLL 2 MDS and 3 NHL.

Comparisons were made between patients requiring hospitalization and patients being followed up at home and the data are shown in Table 3. The hospitalized patients were seen to be significantly older ($p < 0.05$) and there was no significant difference in gender distribution ($p > 0.05$). DM and COPD presence was significantly higher in the hospitalized group than the non-hospitalized group ($p < 0.05$). Leukocyte, neutrophil, lymphocyte and monocyte counts did not differ significantly between the groups

Table 1 Clinical data of patients on the course of COVID-19 infection

The age of the patient at the time of covid-19 diagnosis, median (min–max)	60 (27–93)
Sex, n (%)	
Female	37 (48.1%)
Male	40 (51.9%)
Comorbidity n (%)	
No	31 (40.3%)
Yes	46 (59.7%)
Comorbidities, n	
Hypertension	28
Diabetes	22
CAD	13
Congestive heart failure	2
Hyperlipidemia	10
Lung disease (COPD, asthma)	14
CKD (eGFR < 60 mL/min)	1
Chronic hepatitis	2
Rheumatoid arthritis	2
History of other malignancy	2
COVID PCR, n (%)	
Positive (+)	67 (87.0%)
Negative (–)	10 (13.0%)
Symptom, n (%)	
Yes	56 (72.7%)
No	21 (27.3%)
Symptoms, n (%)	
Fever	47 (81%)
Cough	43 (74%)
Dyspnea	19 (33%)
Weakness	40 (69%)
Arthralgia	13 (22%)
Myalgia	9 (16%)
Loss of taste and smell	5 (9%)
Throat sore	4 (7%)
Headache	4 (7%)
Thorax CT finding, n (%)	
Yes	36 (46.8%)
No	41 (53.2%)
Hospitalization, n (%)	
Yes	39 (50.6%)
No	38 (49.4%)
Median length of stay in the hospital, days (min–max)	8 (2–30)
Need for intensive care, n (%)	
Yes	16 (20.8%)
No	61 (79.2%)
Invasive mechanical ventilation, n (%)	
Yes	16 (20.8%)
No	61 (79.2%)

Table 1 (Continued)

Severity of infection, n (%)	
Mild	38 (49%)
Moderate	21 (27%)
Severe	18 (24%)
Recovery, n (%)	61 (79.2%)
Mortality, n (%)	16 (20.8%)
Treatment, n (%)	
Favipravir	72 (94%)
Hydroxychloroquine	11 (14%)
Pulse corticosteroids	4 (5%)
Tocilizumab	1 (1%)
Anakinra	1 (1%)
Convalescent plasma	3 (4%)
IVIg	2 (3%)
Unknown	2 (3%)
CAD coronary artery disease, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease, COVID-19 coronavirus disease 2019, CT computerized tomography, eGFR estimated glomerular filtration rate, IVIG intravenous immunoglobulin, PCR polymerase chain reaction	

Table 2 Demographic and clinical data of the patients regarding their hematological diagnosis

Diagnosis, n (%)	
Acute lymphoblastic leukemia	2 (2.6%)
Acute myeloid leukemia	5 (2.6%)
Non-Hodgkin lymphoma	15 (19.5%)
Hodgkin lymphoma	5 (6.5%)
Chronic lymphocytic leukemia	11 (14.3%)
Chronic myeloid leukemia	3 (3.9%)
Myeloproliferative neoplasms (Ph negative)	17 (22.1%)
Myelodysplastic syndrome	7 (9.1%)
Multiple myeloma	12 (15.6%)
Age median (min–max)	59 (25–91)
Hematological disease duration, median years (min–max)	2 (0–16)
Disease status at the time of COVID-19 diagnosis, n (%)	
Initial diagnosis or first-line treatment	8 (10.4%)
Remission/watch & wait	41 (53.2%)
Stable	19 (24.7%)
Relapsed/refractory	9 (11.7%)
Active chemotherapy/immunotherapy/immunosuppression at the time of COVID-19 diagnosis, n (%)	
Yes	43 (55.8%)
No	34 (44.2%)
COVID-19 coronavirus disease 2019, Ph Philadelphia chromosome	

who were hospitalized and not. Platelet value and hemoglobin value were significantly lower ($p < 0.05$) in the hospitalized group than in the non-hospitalized group.

Comparisons were made between the survivor and non-survivor patients and the data are given in Table 4. No statistically significant difference was determined between the survivor and non-survivor groups in respect of age and gender distribution or the presence of any comorbidity and rates of HT,

Table 3 Clinical characteristics of hospitalized and non-hospitalized patients

	Hospitalized	Non-hospitalized	<i>p</i>
Age of the patient at the time of COVID-19 diagnosis (median, year)	67	54.5	0.006^a
Gender, <i>n</i> (%)			0.427 ^c
Female	17 (43.6%)	20 (52.6%)	—
Male	22 (56.4%)	18 (47.4%)	—
Comorbidity, <i>n</i> (%)			0.209 ^c
Yes	26 (33.3%)	18 (47.4%)	—
No	13 (66.7%)	20 (52.6%)	—
Hypertension	18 (46.2%)	14 (36.8%)	0.407 ^c
Diabetes	14 (35.9%)	4 (10.5%)	0.009^c
COPD	11 (28.2%)	3 (7.9%)	0.021^c
Hematological diagnosis, <i>n</i> (%)			
ALL	1 (2.6%)	1 (2.6%)	1.000 ^c
AML	2 (5.1%)	3 (7.9%)	0.622 ^c
NHL	9 (23.1%)	6 (15.8%)	0.420 ^c
HL	0 (0.0%)	5 (13.2%)	0.019^c
CLL	8 (20.5%)	3 (7.9%)	0.114 ^c
CML	1 (2.6%)	2 (5.3%)	0.615 ^c
MPN	6 (15.4%)	11 (28.9%)	0.151 ^c
MDS	6 (15.4%)	1 (2.6%)	0.052 ^c
MM	6 (15.4%)	6 (15.8%)	0.961 ^c
Disease status at the time of COVID-19 diagnosis, <i>n</i> (%)			
Initial diagnosis/first-line treatment	7 (17.9%)	1 (2.6%)	0.028^c
Remission/watch & wait	17 (43.6%)	24 (63.2%)	0.085 ^c
Stable	10 (25.6%)	9 (23.7%)	0.842 ^c
Relapsed/refractory	5 (12.8%)	4 (10.5%)	0.754 ^c
Active treatment at the time of COVID-19 diagnosis, <i>n</i> (%)			0.139 ^c
Yes	25 (35.9%)	18 (47.4%)	—
No	14 (64.1%)	20 (52.6%)	—
Symptom, <i>n</i> (%)			0.000^c
Yes	36 (92.3%)	20 (52.6%)	—
No	3 (7.7%)	18 (47.4%)	—
Thorax CT finding, <i>n</i> (%)			0.000^c
Yes	34 (87.2%)	2 (5.3%)	—
No	5 (12.8%)	36 (94.7%)	—
Wbc ($\times 10^9/L$) median (range)	4.1 (0.1–83.0)	5.6 (0.1–68.0)	0.117 ^b
Neu ($\times 10^9/L$) median (range)	2.1 (0.0–55.0)	3.4 (0.0–14.3)	0.154 ^b
Lym ($\times 10^9/L$) median (range)	0.7 (0.0–36.8)	1.5 (0.0–61.9)	0.094 ^b
Hb (gr/dL) median (range)	10 (6–15)	13 (6–16)	0.002^b
Plt ($\times 10^9/L$) median (range)	126 (4–587)	239 (17–635)	0.018^b

ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, CLL chronic lymphocytic leukemia, CML chronic myeloid leukemia, COPD chronic obstructive pulmonary disease, COVID-19 coronavirus disease 2019, CT computerized tomography, Hb hemoglobin, HL hodgkin lymphoma, Lym lymphocyte, MDS myelodysplastic syndrome, MM multiple myeloma, MPN myeloproliferative neoplasms, Neu neutrophil, NHL non-Hodgkin lymphoma, Plt platelet, Wbc white blood cell count

^aIndependent sample t test
^bMann–Whitney U test
^c χ^2 test (Fischer test)

Table 4 Clinical characteristics of survivors and non-survivors

	Non-survivor (<i>n</i> = 16)	Survivor (<i>n</i> = 61)	<i>p</i>
Age of the patient at the time of COVID-19 diagnosis (median, years)	70.5	59.0	0.077 ^a
Gender, <i>n</i> (%)			0.861 ^c
Female	8 (50%)	29 (47.5%)	—
Male	8 (50%)	32 (52.5%)	—
Comorbidity, <i>n</i> (%)			0.143 ^c
Yes	7 (43.8%)	39 (63.9%)	—
No	9 (56.3%)	22 (36.1%)	—
Hypertension	4 (25.0%)	28 (45.9%)	0.131 ^c
Diabetes	4 (25.0%)	14 (23.0%)	0.863 ^c
COPD	2 (12.5%)	12 (19.7%)	0.508 ^c
Hematological diagnosis, <i>n</i> (%)			
ALL	0 (0.0%)	2 (3.3%)	1.000 ^c
AML	2 (12.5%)	3 (4.9%)	0.276 ^c
NHL	3 (18.8%)	12 (19.7%)	0.934 ^c
HL	0 (0.0%)	5 (8.2%)	0.577 ^c
CLL	4 (25.0%)	7 (11.5%)	0.169 ^c
CML	0 (0.0%)	3 (4.9%)	1.000 ^c
MPN	3 (18.8%)	14 (23.0%)	0.718 ^c
MDS	2 (12.5%)	5 (8.2%)	0.631 ^c
MM	2 (12.5%)	10 (16.4%)	0.702 ^c
Disease status at the time of COVID-19 diagnosis, <i>n</i> (%)			
Initial diagnosis/first-line treatment	3 (18.8%)	5 (8.2%)	0.352 ^c
Remission/watch & wait	5 (31.3%)	36 (59.0%)	0.048^c
Stable	4 (25.0%)	15 (24.6%)	0.973 ^c
Relapsed/refractory	4 (25.0%)	5 (8.2%)	0.083 ^c
Active treatment at the time of COVID-19 diagnosis, <i>n</i> (%)			0.597 ^c
Yes	8 (50.0%)	35 (57.4%)	—
No	8 (50.0%)	26 (42.6%)	—
Symptom, <i>n</i> (%)			0.034^c
Yes	15 (93.8%)	41 (67.2%)	—
No	1 (6.3%)	20 (32.8%)	—
Thorax CT finding, <i>n</i> (%)			0.000^c
Yes	15 (93.8%)	21 (34.4%)	—
No	1 (6.3%)	40 (65.6%)	—
Wbc ($\times 10^9/L$) median (range)	3.1 (0.1–59.9)	5.6 (0.1–83.0)	0.232 ^b
Neu ($\times 10^9/L$) median (range)	1.8 (0.0–21.4)	3.3 (0.0–55.0)	0.263 ^b
Lym ($\times 10^9/L$) median (range)	0.7 (0.0–36.8)	1.2 (0.0–61.9)	0.696 ^b
Hb (gr/dL) median (range)	8 (6–13)	12 (6–16)	0.003^b
Plt ($\times 10^9/L$) median (range)	54 (10–588)	204 (4–635)	0.002^b
Hospitalization, <i>n</i> (%)			0.000^c
Yes	16 (100.0%)	23 (37.7%)	—
No	0 (0.0%)	38 (62.3%)	—
Number of days of hospitalization (median)	6	9	0.923 ^b
Need for intensive care, <i>n</i> (%)			0.000^c
Yes	13 (81.3%)	3 (4.9%)	—
No	3 (18.7%)	58 (95.1%)	—

Table 4 (Continued)

	Non-survivor (n = 16)	Survivor (n = 61)	p
<i>Invasive mechanical ventilation, n (%)</i>			0.000^c
Yes	15 (93.8%)	1 (1.6%)	–
No	1 (6.3%)	60 (98.4%)	–

ALL acute ALL, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CLL* chronic lymphocytic leukemia, *CML* chronic myeloid leukemia, *COPD* chronic obstructive pulmonary disease, *COVID-19* coronavirus disease 2019, *CT* computerized tomography, *Hb* hemoglobin, *HL* hodgkin lymphoma, *Lym* lymphocyte, *MDS* myelodysplastic syndrome, *MM* multiple myeloma, *MPN* myeloproliferative neoplasms, *Neu* neutrophil, *NHL* non-Hodgkin lymphoma, *Plt* platelet, *Wbc* white blood cell count
^aIndependent sample t test
^bMann–Whitney U test
^c χ^2 test (Fischer test)

DM or COPD ($p > 0.05$ for all). No significant difference was determined between the survivor and non-survivor groups in respect of leukocyte, neutrophil, lymphocyte and monocyte values ($p > 0.05$). Platelet count and hemoglobin count were significantly lower in the group with mortality than in the group with recovery ($p < 0.0$).

Discussion

Most patients with blood cancer have a suppressed immune system because of the biology of the malignancy itself and cancer treatments. Although current chemotherapy, radiotherapy and other immunosuppressive treatments increase the quality of life of patients with hematological cancers and prolong their overall survival, they also suppress the cellular and humoral immunity of patients, thereby making them vulnerable to infections. Moreover, the advanced age of most of these patients and their comorbidities also increase the risk of infection [8, 9]. In this context, it can be thought that the course of COVID-19 may be more aggressive and mortality may be higher in patients with hematological malignancies.

In a previous study, COVID-19 was most commonly detected in patients with CLL (39.4%) and MM (33.3%) [7]. The ASH Research Collaborative COVID-19 Registry reported that acute leukemia (33%), NHL (27%) and myeloma or amyloidosis (16%) were the most common blood cancers in patients diagnosed with COVID-19 [10]. In this study, COVID-19 was most commonly seen in patients with MPN, NHL, and MM respectively. Although patients with MPN have less immunosuppression, in the context of this study, the most frequent occurrence of COVID-19 in this group is probably due to the high percentage of MPN cases among the hematological malignancies.

The majority of patients with COVID-19 infection are asymptomatic or have mild to moderate symptoms. Cough, fever, dyspnea, musculoskeletal symptoms (myalgia, joint pain, fatigue) are the most frequently reported symptoms [11, 12]. The most common symptoms in the patients in this study were fever,

weakness, and cough, similar to the general population. In previous studies, the rate of asymptomatic cases has been reported to be around 56–58% [13, 14]. In our study, most of the cases were symptomatic and the rate of asymptomatic patients was 27.3%; 50.6% of patients were hospitalized, with a higher rate determined in patients with hypertension and COPD and in older patients.

Severe pneumonia develops in 15% of patients and 5% of patients need intensive care unit (ICU) management [15]. In this study, the need for invasive mechanical ventilation (20.8%) and follow-up in ICU (20.8%) was found to be higher in patients with hematological cancer compared to non-cancer cases described in the literature.

In studies involving patients with hematological cancer, COVID-19 mortality has been reported in the range of 32 to 61% [16, 17]. In our study, mortality developed in 16 of the total 77 patients at a mortality rate of 20.8%. Compared with the literature, the mortality rate in this study was lower than that of patients with hematological cancer, but higher than that of the healthy population [15]. The reason for this may be bone marrow suppression and cytopenia, chemotherapy and the immunosuppressive agents used in the treatment of hematological cancer patients.

In patients with hematological cancer, risk factors such as age, comorbidities and the severity of COVID-19 clinical course have been reported to be associated with mortality [18]. In the comparison of this study's surviving and non-surviving patients, as expected, mortality was higher in patients who were symptomatic, had thorax CT findings, were intubated and were transferred to the intensive care unit.

Interestingly, disease subtype, disease state, comorbidity and age were not found to have an effect on mortality in this study. A large, population-based, Spanish study showed that diagnosis of AML and MDS was related to mortality [19]. In a study from Italy, advanced age, progressive hematological disease, and severe COVID-19 pneumonia were stated as risk factors for mortality [7]. Cattaneo et al. determined that the status of receiving active chemotherapy or immunosuppressive was the most important parameter associated with the risk of death [20]. The heterogeneity of the hematological diagnoses of the patients and the treatments given made it difficult to analyze the effect of treatment on mortality.

In this study, it was observed that low hemoglobin and low platelet count were associated with both hospitalization and mortality. Similarly, in a previous review, it was stated that a decrease in platelet count was associated with mortality [21]. In a study by Shang et al., platelet levels were found to be lower in patients with severe disease [22]. Another retrospective single-center study demonstrated that thrombocytopenia was related with mortality in patients with COVID-19 [23]. According to the same study results, as the

platelet counts decreased, the mortality rate increased [24].

Thrombopoetin, which is released from the liver in response to infection, may help prevent lung specific entry by increasing the lung megakaryocytes in the lungs and increasing the number of platelets. According to this hypothesis, in patients with decreased platelet count, it is easier for the virus to enter the lungs, thereby explaining the relationship of severe pneumonia with mortality. It is also known that in severe pulmonary involvement, endothelial damage triggers thrombocyte activation and aggregation and this may cause platelet depletion [25]. Furthermore, this information may explain the low platelet counts in patients with mortality. However, bone marrow suppression or therapy-related thrombocytopenia, which are common in patients with hematological cancer, also confuse the results.

In this study, low hemoglobin levels were also found to be associated with mortality. In a study of 1099 COVID-19 cases, patients with anemia had worse clinical outcomes [26]. In another study, it was shown that low hemoglobin levels were associated with severe disease [27]. Many studies have shown that anemia worsens the course of pulmonary diseases and increases mortality [28, 29]. The reason for the higher mortality of patients with COVID-19 with low hemoglobin may be that oxygenation is impaired in anemia and tissue hypoxia aggravates the infection and that anemic patients are both older and tend to be patients with comorbidities. Low hemoglobin levels were seen to be common in the current study group with hematological cancer.

There were some limitations to this study, primarily the retrospective design and that it was conducted in a single center with a small number of patients so it is difficult to generalize the results.

Take-home message

- The aim of this study was to examine the course of COVID-19 (coronavirus disease 2019) in patients with hematological malignancies and to determine the factors affecting the severity of the infection.
- It should be kept in mind that low hemoglobin and platelet levels contribute to mortality. In addition, it is important to protect patients with hematological cancer from COVID-19 infection and undertake effective vaccination due to its more aggressive and mortal course than for patients without a malignancy.
- Further studies and long-term observations are required with a larger number of patients to determine predictive factors associated with the severity of the clinical course and mortality.

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Declarations

Conflict of interest P. Tığlıoğlu, M. Albayrak, M. Tığlıoğlu, H.B.A. Öztürk, M.R. Aras, B. Sağlam and S. Maral declare that they have no competing interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Ethical standards All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Approval for this study was granted by the Republic of Turkey Ministry of Health and the Local Ethics Committee.

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